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Clinical Benefit of *Nanoparticle Albumin-Bound-Paclitaxel* in Recurrent/Metastatic Head and Neck Squamous Cell Carcinoma Resistant to Cremophor-Based Paclitaxel or Docetaxel

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Abstract

Background: The clinical benefit of *nab*-paclitaxel monotherapy for recurrent/metastatic head and neck squamous cell carcinoma (RM-HNSCC) that progressed on other taxanes (cremophor-based paclitaxel or docetaxel) is unknown.

Methods: A retrospective analysis of patients treated at a single institution with *nab*-paclitaxel for taxane-resistant RM-HNSCC. The exploratory hypothesis was that *nab*-paclitaxel would result in clinical benefit (tumor response) in patients with taxane-resistant RM-HNSCC.

Results: Twelve patients who were treated with *nab*-paclitaxel monotherapy for taxane-resistant RM-HNSCC and met all eligibility criteria were identified. The majority of patients (n=9; 75%) received 3 or more lines of therapy for RM-HNSCC. All patients had platin-resistant and ten patients (83%) had cetuximab-resistant disease. Patients had RM-HNSCC that progressed on cremophor-based paclitaxel (8), docetaxel (1), or both (3). With prior taxane, the best tumor response was partial (PR) in 4 patients (33%), stable (SD) in 3 (25%), and progression in 5 (42%). The median time-to-progression (TTP) with prior taxane was 1.7 (range, 0.7–9.0) months. The median interval from last dose of taxane to first dose of *nab*-paclitaxel was 3 (0.7–31.3) months. With *nab*-paclitaxel, tumor response occurred in two patients (17%; PR in both) and disease control (PR and SD) occurred in five (42%). Median TTP with *nab*-paclitaxel was 2.1 months (range: 0.6–6.2) and median overall survival was 4.9 months (range: 1.9–13.5).

Conclusion: *nab*-Paclitaxel provided clinical benefit in some patients with taxane-resistant RM-HNSCC. The median TTP with *nab*-paclitaxel and with prior taxane were similar. This exploratory observation warrants further investigation in prospective studies.

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All other authors (Jessica Ley, Dr. Tanya Wildes, Kristin Daly and Dr. Peter Oppelt) declare that they have no conflict of interest.

Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Keywords

Clinical Benefit; *nab*-Paclitaxel; cremophor-based paclitaxel; recurrent/metastatic HNSCC

Introduction

Most patients with head and neck squamous cell carcinoma (HNSCC) present with locally advanced disease that is treated with curative intent. However, even with intensive multimodality therapy, development of recurrent or metastatic (RM) disease persists to be a frequent event. The Erbitux in First-Line Treatment of Recurrent or Metastatic Head and Neck Cancer (EXTREME) trial established a platin agent (cisplatin or carboplatin), 5-fluorouracil, and cetuximab (PF-C) as the current optimal first-line therapy for RM-HNSCC [1]. Overall survival (OS) was improved with the addition of cetuximab to PF. Median OS of patients treated with PF-C was 10.1 months, median progression-free survival (PFS) 5.6 months, and tumor response rate was 36%.

Alternative treatment options to PF-C for patients with RM-HNSCC are limited [2]. Docetaxel [3,4], methotrexate [4–7], or pemetrexed [8] resulted in tumor response rates of 6–27%. Recently, the CheckMate-141 randomized phase III trial showed that nivolumab, a programmed death receptor-1 (PD-1) inhibitor, improved tumor response rate (13.3 vs 5.8%) and OS (7.5 vs 5.1 months) over investigator's choice (docetaxel, methotrexate, or cetuximab) in patients with platin-resistant HNSCC [9]. The KEYNOTE-012 phase Ib trial showed that pembrolizumab, a PD-1 inhibitor, is also an active agent in patients with RM-HNSCC [10].

Cremophor-based paclitaxel has significant activity in RM-HNSCC. A phase II trial conducted by the Eastern Cooperative Oncology Group (ECOG PA 390) showed that paclitaxel monotherapy given as first line treatment resulted in a tumor response rate of 40% [11]. In RM-HNSCC, a dose-response relationship of paclitaxel does not exist across the usual dose range (135 and 200 mg/m²/cycle), with equivalent tumor response rates and OS between low and high doses [12].

Cross-resistance among taxanes occurs in many cancers. The mechanisms of cross-resistance are complex and vary based on taxane type [13]. Cross-resistance to taxanes may be partial and dynamic, as demonstrated by better tumor response of breast cancer after longer vs shorter intervals from prior taxane exposure and with acquired versus primary resistance [14].

Nanoparticle albumin-bound (*nab*-) paclitaxel may improve drug delivery to tumor tissue compared to cremophor-based paclitaxel [15–16]. Macropinocytosis, the process by which macromolecules like albumin are taken up into cells, is upregulated in the setting of activated epidermal growth factor receptor (EGFR), RAS or PI3K pathways [16]. Activation of these pathways are common events in HNSCC [17–22]. Collectively, these data suggest that *nab*-paclitaxel could be a more effective therapy than cremophor-based paclitaxel in HNSCC.

In patients with HNSCC treated with curative intent, we reported the efficacy of a novel induction chemotherapy regimen that included *nab*-paclitaxel followed by concurrent high dose bolus cisplatin and radiation therapy (CRT) [23]. Most patients were smokers with bulky T3/4 and N2/3 tumors. With a median follow-up of 59 months, relapse occurred in only 5 (17%) patients. Two-year disease-specific survival (DSS) was 100% in human papillomavirus (HPV)-related oropharyngeal (OP) SCC and 91% in HPV-unrelated HNSCC. Two-year OS was 94% in HPV-related OPSCC and 83% in HPV-unrelated HNSCC. Efficacy outcomes of patients treated with this *nab*-paclitaxel-containing induction regimen followed by CRT were better than those of a historical group treated with a docetaxel-containing regimen followed by CRT [24]. A subsequent study in similar patients confirmed the low relapse risk with *nab*-paclitaxel-based induction chemotherapy and CRT [25].

In RM-HNSCC, there are no published prospective trials that evaluated the clinical benefit of *nab*-paclitaxel monotherapy. Also, no clinical literature exists on the topic of taxane cross-resistance in patients with RM-HNSCC. In the absence of such data, we performed a retrospective analysis of our institution's experience of *nab*-paclitaxel in patients with RM-HNSCC that was resistant to cremophor-based paclitaxel or docetaxel (hereafter, collectively called taxane). The objectives of this exploratory analysis were to determine the tumor response rate and time-to-progression (TTP) with *nab*-paclitaxel in taxane-resistant RM-HNSCC.

Materials and Methods

Patient Selection

This retrospective study was approved by the Institutional Review Board (IRB). Signed informed consent by patients was not required. Patients were identified from the panel of patients with RM-HNSCC treated at Washington University from April 2014 to January 2015 (the interval that *nab*-paclitaxel monotherapy was used in this setting). Inclusion criteria for eligible patients included RM-HNSCC of the oropharynx, larynx, hypopharynx, oral cavity, or nasopharynx that was resistant to taxane and was subsequently treated with *nab*-paclitaxel monotherapy. Resistance to taxane was defined as disease progression as assessed by RECIST [26] during therapy with either cremophor-based paclitaxel or docetaxel administered for treatment of RM-HNSCC. Exclusion criteria included non-SCC histology, other sub-sites of SCC (cutaneous, para-nasal sinuses, salivary), or RM-HNSCC treated with a combination therapy that included *nab*-paclitaxel.

Study Design

Data were retrospectively extracted from patient charts and electronic medical records. Data collected on eligible patients included patient, tumor, and treatment characteristics. Patient characteristics included age, gender, and smoking history. Tumor characteristics included initial cancer staging (TNM), primary tumor site and HPV status (if OPSCC) based on the surrogate marker p16^{INK4a} by immunohistochemistry (IHC). Treatment characteristics included prior curative therapy (type), interval from curative therapy to RM-HNSCC, prior systemic therapy for RM-HNSCC (number of lines and type), prior taxane with curative therapy (type, interval from taxane to *nab*-paclitaxel for RM-HNSCC), and prior taxane for

RM-HNSCC (type and schedule, best tumor response by RECIST to taxane, interval from taxane to *nab*-paclitaxel for RM-HNSCC).

Additional treatment characteristics collected during treatment of RM-HNSCC with *nab*-paclitaxel included: line of therapy for RM-HNSCC, number of cycles, best tumor response by RECIST, TTP from first dose of *nab*-paclitaxel until progression by RECIST, PFS from first dose of *nab*-paclitaxel until progression or death, and OS from first dose of *nab*-paclitaxel until death. Follow-up data collected included cause of death (HNSCC, treatment-related mortality [TRM], co-morbidity, unknown) and lost to follow-up (yes/no).

Endpoints, Hypotheses, and Statistical Analysis

Endpoints of interest included best tumor response by RECIST to *nab*-paclitaxel (complete [CR], partial [PR], stable [SD], or progression [PROG]), disease control (for CR, PR, and SD), TTP, PFS, and OS. TTP and OS were determined from date of first dose of *nab*-paclitaxel for treatment of RM-HNSCC until date of event (progression, death, or alive at last follow-up). The exploratory hypothesis was that *nab*-paclitaxel would result in tumor responses in taxane-resistant RM-HNSCC.

Descriptive statistical methods were used for analyses of patient, tumor, and treatment characteristics. Kaplan-Meier (KM) methods were used to analyze TTP and OS.

Results

Patient, Tumor, and Treatment Characteristics

Twelve patients were identified to have been treated with *nab*-paclitaxel monotherapy for taxane-resistant RM-HNSCC and met all eligibility criteria for the retrospective analysis. The characteristics of these patients are summarized in Table 1. Most patients were male, smokers, and had oropharynx or larynx SCC. Five patients had p16^{INK4a} positive OPSCC. The majority of patients (n=9; 75%) received 3 or more lines of therapy for RM-HNSCC. All patients had platin-resistant disease and ten of twelve patients (83%) had cetuximab-resistant disease.

Prior Taxane Exposure for RM-HNSCC

Patients had RM-HNSCC that had progressed on cremophor-based paclitaxel (8), docetaxel (1), or both (3). The schedule of administration of prior taxane was every three week cycles in all patients. The best tumor response to prior taxane was PR in 4 patients (33%), SD in 3 (25%), and progression in 5 (42%). The median TTP and PFS with prior taxane were 1.7 (0.7–9.0) months. The median interval (range) from last dose of taxane to first dose of *nab*-paclitaxel was 3 (0.7–31.3) months.

Clinical Benefit of *nab*-Paclitaxel in Taxane-Resistant RM-HNSCC

Tumor response with *nab*-paclitaxel monotherapy occurred in two patients (17%; PR in both) and disease control (PR and SD) occurred in five patients (42%). Figure 1 shows the tumor response with *nab*-paclitaxel in the two cases of a PR. Median TTP and PFS for the

12 patients treated with *nab*-paclitaxel were 2.1 months (range: 0.6–6.2) [Figure 2], and median OS was 4.9 months (range: 1.9–13.5) [Figure 3].

Of the 8 patients with disease progression as best response to prior taxane, 3 (37.5%) experienced disease control (1 PR and 2 SD) with *nab*-paclitaxel. The median TTP with *nab*-paclitaxel was 1.9 months (range: 0.6–6.2) in these 8 patients. Of the 4 patients with disease control as best response to prior taxane, 2 (50%) experienced disease control (1 PR and 1 SD) with *nab*-paclitaxel. The median TTP with *nab*-paclitaxel was 2.5 months (range: 1.1–4.0) in these 4 patients.

The interval from prior taxane to *nab*-paclitaxel was 3 months in 6 patients, of which 2 patients (33%) experienced disease control (both SD) with *nab*-paclitaxel. The median TTP with *nab*-paclitaxel was 1.7 months (range: 0.6–4.0) in these patients. The interval from prior taxane to *nab*-paclitaxel was >3 months in 6 patients, of which 3 (50%) patients experienced disease control (2 PR and 1 SD) with *nab*-paclitaxel. The median TTP with *nab*-paclitaxel was 2.7 months (range: 1.0–6.2) in these patients.

Discussion

In this report, we describe, for the first time, the activity of *nab*-paclitaxel in taxane-resistant RM-HNSCC. In these patients, *nab*-paclitaxel monotherapy resulted in a tumor response rate of 17% and disease control rate of 42%. Although the median TTP was only 2.1 months (range: 0.6–6.2) with *nab*-paclitaxel, some patients did experience disease control for 3 or more months. Additionally, the median TTPs with *nab*-paclitaxel and with prior taxane (1.7; range: 0.7–9 months) were similar. The activity of *nab*-paclitaxel is particularly noteworthy given that most patients also had platin- and cetuximab-resistant disease. In comparison, the median TTP for second line therapy with docetaxel was 2.1 months³ and with methotrexate was 1.7 months [6]. These data support that *nab*-paclitaxel may provide clinical benefit in taxane-resistant RM-HNSCC.

The anti-tumor mechanism of *nab*-paclitaxel in taxane-resistant RM-HNSCC is not known. One mechanism of taxane-resistance is reduced cellular concentration of taxane due to alterations in cell membrane transporters such as p-glycoprotein [13]. Nanoparticle albumin-bound (*nab*-) paclitaxel may improve drug delivery to tumor tissue compared to cremophor-based paclitaxel [15–16]. Macropinocytosis is an important process that promotes the internalization of extracellular albumin, and most likely, *nab*-paclitaxel, into cells. Albumin is a key source of energy and nutrients for cells. Macropinocytosis can be driven by signaling through the EGFR and PI3 kinase. Both signaling pathways are important in the biology of HNSCC [27–32]. The mechanism of activity of *nab*-paclitaxel in taxane-resistant RM-HNSCC may relate to the upregulation of macropinocytosis, driven by activation of the EGFR and PI3 kinase pathways, which increase the uptake of *nab*-paclitaxel into tumor cells and result in cytotoxicity.

Other mechanisms may explain the efficacy of *nab*-paclitaxel in taxane-resistant RM-HNSCC. Although a dose-response relationship of cremophor-based paclitaxel does not exist in RM-HNSCC across the usual dose range (135–200 mg/m²/cycle) [12], the

relationship between schedule of administration of paclitaxel and tumor response has not been evaluated. In breast cancer, weekly administration of cremophor-based paclitaxel was superior to an every three week schedule [33,34]. In our study, prior taxanes were given on an every three week schedule, but upon disease progression *nab*-paclitaxel was given on a weekly schedule. It is possible that the change in schedule may be a mechanism of efficacy of *nab*-paclitaxel in taxane-resistant RM-HNSCC.

Some studies suggest that *nab*-paclitaxel may be more efficacious than cremophor-based paclitaxel or docetaxel in selected cancers. Several reports have documented the superior efficacy of *nab*-paclitaxel over cremophor-based paclitaxel or docetaxel in advanced breast cancer [35,36]. Similarly, *nab*-paclitaxel was more efficacious than cremophor-based paclitaxel in advanced non-small cell lung cancer, particularly squamous histology [37]. A direct comparison of *nab*-paclitaxel to cremophor-based paclitaxel or docetaxel has not been performed in RM-HNSCC.

Cross-sensitivity of taxanes has been described in other cancers. Cremophor-based paclitaxel is active in docetaxel-resistant breast cancer, with a response rate of 19.5% [14]. Docetaxel is active in cremophor-based paclitaxel-resistant breast cancer, with a response rate of 18.1% [38]. These response rates are similar to that seen in our study with *nab*-paclitaxel in taxane-resistant RM-HNSCC.

Our study has several limitations. This is a retrospective study of a limited number of patients. A larger, prospective study is required to confirm the efficacy signal seen in this report. Also, we are unable to assess the influence of the schedule of *nab*-paclitaxel administration on efficacy since cremophor-based paclitaxel or docetaxel were given on an every three week schedule, and the *nab*-paclitaxel was given every week.

In conclusion, *nab*-paclitaxel provided clinical benefit to some patients in taxane-resistant RM-HNSCC. This exploratory observation warrants further investigation in prospective studies.

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a.

b.

Fig. 1.

CT scan images of two patients with taxane-resistant RM-HNSCC showing tumor response with *nab*-paclitaxel monotherapy

a) CT images showing progression of a target lesion in the right lung between cycles 9 and 12 of cremophor-based paclitaxel followed by response of the same target lesion with *nab*-paclitaxel given as sixth line therapy for RM-HNSCC

b) CT images showing response of a target lesion in the right hepatic lobe with *nab*-paclitaxel given as seventh line therapy for RM-HNSCC

Fig. 2.
Time-to-Progression of 12 patients with taxane-resistant RM-HNSCC treated with *nab*-paclitaxel

Fig. 3.
Overall Survival of 12 patients with taxane-resistant RM-HNSCC treated with *nab*-paclitaxel

Table 1:

Patient, Tumor and Treatment Characteristics

Characteristic	Outcome (n=12 patients)
Age (years)	
Mean	56
Range	44–79
Sex	
M	10
F	2
Smoking History	
Yes	8
No	4
Primary Site	
Oropharynx	5
Larynx	5
Hypopharynx	1
Nasopharynx	1
p16^{INK4a}	
Negative	7
Positive	5
Prior Therapy for Curative Disease^a	
Cisplatin and RT	4
Cetuximab and RT	2
RT alone	2
None	1
Interval from Curative to RM Treatment	
Mean	16
Range (mos.)	3–53
Prior Therapy for RM-Disease	
Platin	12
Cetuximab	10
Taxane ^b	12
Lines of Prior Therapy for RM-HNSCC	
4	6
3	3
1–2	3

^a 3 of the 12 patients presented with metastatic (stage IVC) at diagnosis and 1 other patient declined curative therapy.

^b 3 of the 12 patients received both cremophor-based paclitaxel and docetaxel in sequence.

Table 2:

Prior Taxane for RM-HNSCC

Characteristic	Outcome (n=12 patients)
Prior Taxane for RM-Disease	
Cremophor-based paclitaxel (135 mg/m ² q 3 weeks)	11
Docetaxel (75 mg/m ² q 3 weeks)	4
Best Tumor Response to Prior Taxane	
Complete	0
Partial	3
Stable	4
Progression	5
Time to Progression on Prior Taxane	
Median (mos.)	1.7
Range	0.7–9.0
Interval from Prior Taxane to <i>nab</i>-Paclitaxel	
Median (mos.)	3
Range	0.7–31.3

Table 3:Efficacy of *nab*-Paclitaxel Monotherapy for RM-HNSCC

Characteristic	Outcome (n=12 patients)
Best Tumor Response to <i>nab</i>-Paclitaxel	
Partial	2
Stable	3
Progression	7
Time to Progression	
Median	2.1
Range (mos.)	0.6–6.2
Progression Free Survival	
Median	2.1
Range (mos.)	0.6–6.2
Overall Survival	
Median	4.9
Range (mos.)	1.9–13.5